Resilience as a Research Priority
A Perspective from NIA

Basil Eldadah, MD, PhD
Division of Geriatrics and Clinical Gerontology
NIA

Clin-STAR Annual Meeting
November 16, 2022

Recent NIA-Sponsored Initiatives on Resilience

- **RFA-AG-17-040:** Short-term Measurements of Physical Resilience as a Predictor of Healthspan in Mice (R01) http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-040.html
- **RFA-AG-17-014:** Predictors and Determinants of Age-Related Changes in Resiliencies to Physical Stressors in Humans (UH2/UH3) http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-014.html
- **RFA-AG-17-061:** Interdisciplinary Research to Understand the Complex Biology of Resilience to Alzheimer's Disease Risk (R01) https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-061.html
- **PAR-16-326:** Advancing Basic Behavioral and Social Research on Resilience: An Integrative Science Approach (UH2/UH3) http://grants.nih.gov/grants/guide/pa-files/PAR-16-326.html
- **RFA-AG-18-024**: Collaboratory on Research Definitions for Cognitive Reserve and Resilience to Alzheimer's Disease (R24) https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-18-024.html
- **RFA-AG-19-025:** Development of Personalized In Vitro Assays to Quantitatively Assess Age-related Changes in Cellular Resiliencies to Physiologic Stressors (R43/R44 Clinical Trial Not Allowed) https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-025.html
- **RFA-AG-19-026:** Development of Personalized In Vitro Assays to Quantitatively Assess Age-related Changes in Cellular Resiliencies to Physiologic Stressors (R41/R42 Clinical Trial Not Allowed) https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-026.html

https://www.nia.nih.gov/resilienceandaging

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 71, No. 11, 1407–1414
doi:10.1093/gerona/glw086
Advance Access publication August 16, 2016

OXFORD

Special Issue: Moving Geroscience Into Uncharted Waters: Perspective

Resilience in Aging Mice

James L. Kirkland,[1] Michael B. Stout,[1] and Felipe Sierra[2]

[1]Mayo Clinic Kogod Center on Aging, Mayo Clinic, Rochester, Minnesota. [2]Division of Aging Biology, National Institute on Aging, National Institutes of Health, Bethesda, Maryland.

Address correspondence to Felipe Sierra, PhD, Division of Aging Biology, National Institute on Aging, National Institutes of Health, 7201 Wisconsin Avenue, Gateway Building, Suite 2C231, Bethesda, MD 20892. E-mail: sierraf@nia.nih.gov

Received March 22, 2016; Accepted April 19, 2016

Decision Editor: Rafael de Cabo, PhD

Abstract

Recently discovered interventions that target fundamental aging mechanisms have been shown to increase life span in mice and other species, and in some cases, these same manipulations have been shown to enhance health span and alleviate multiple age-related diseases and conditions. Aging is generally associated with decreases in resilience, the capacity to respond to or recover from clinically relevant stresses such as surgery, infections, or vascular events. We hypothesize that the age-related increase in susceptibility to those diseases and conditions is driven by or associated with the decrease in resilience. Thus, a test for resilience at middle age or even earlier could represent a surrogate approach to test the hypothesis that an intervention delays the process of aging itself. For this, animal models to test resilience accurately and predictably are needed. In addition, interventions that increase resilience might lead to treatments aimed at enhancing recovery following acute illnesses, or preventing poor outcomes from medical interventions in older, prefrail subjects. At a meeting of basic researchers and clinicians engaged in research on mechanisms of aging and care of the elderly, the merits and drawbacks of investigating effects of interventions on resilience in mice were considered. Available and potential stressors for assessing physiological resilience as well as the notion of developing a limited battery of such stressors and how to rank them were discussed. Relevant ranking parameters included value in assessing general health (as opposed to focusing on a single physiological system), ease of use, cost, reproducibility, clinical relevance, and feasibility of being repeated in the same animal longitudinally. During the discussions it became clear that, while this is an important area, very little is known or established. Much more research is needed in the near future to develop appropriate tests of resilience in animal models within an aging context. The preliminary set of tests ranked by the participants is discussed here, recognizing that this is a first attempt.

Keywords: Aging—Resilience—Health Span

Aging, Frailty, and Resilience

Aging is the leading risk factor for many of the chronic diseases that account for the bulk of morbidity, mortality, and health costs in most of the world. Indeed, aging is not merely "a risk factor" for chronic diseases; it often surpasses all other risk factors by one or more orders of magnitude. A common argument is that chronic age-related diseases occur late in life simply because of the time it takes for damage to accumulate. However, a more important reason might be that young organisms have robust defenses against homeostatic insults and challenges. With aging, these defense capabilities decline, contributing to the emergence of diseases that manifest clinically. A few examples of diseases primarily affecting the elderly adult are illustrative. Data from the Framingham study indicate that being 70 years old is, by itself, a higher risk factor for cardiovascular disease than high cholesterol, high blood pressure, and obesity combined (1), and this is because, as aging progresses, the ability of the organism to deal with insults of equal magnitude decreases: resilience is diminished.

A second example includes Alzheimer's and other neurodegenerative diseases. In the case of familial Alzheimer's disease—a small proportion of all cases, but an informative paradigm nevertheless—affected individuals have mutations known to cause Alzheimer's disease inescapably, in genes such as amyloid precursor protein or presenilins (2). However, even though the mutant proteins are present from early in embryogenesis, the disease often does not appear until the fourth or, more often, the fifth decade of life (3), suggesting that age-related changes in inflammation and proteostasis may contribute to declines in resilience.

Finally, in the case of cancer, it is often argued that the disease occurs late in life simply because of the time needed for any single

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2017, Vol. 72, No. 7, 980–990
doi:10.1093/gerona/glx015
Advance Access publication May 5, 2017

OXFORD

Special Article

Report: NIA Workshop on Measures of Physiologic Resiliencies in Human Aging

Evan C. Hadley,[1] George A. Kuchel,[2] Anne B. Newman,[3,4] Heather G. Allore,[5] Jenna M. Bartley,[6] Cindy S. Bergeman,[7] Michael L. Blinov,[8] Cathleen S. Colon-Emeric,[9,10] Firdaus S. Dabhar,[11] Laura L. Dugan,[12] Chhanda Dutta,[1] Basil A. Eldadah,[1] Luigi Ferrucci,[13] James L. Kirkland,[14] Stephen B. Kritchevsky,[15] Lewis A. Lipsitz,[16,17] Neelesh K. Nadkarni,[4] May J. Reed,[18] Kenneth E. Schmader,[19,20] Felipe Sierra,[21] Stephanie A. Studenski,[22] Ravi Varadhan,[23,24] Jeremy D. Walston,[25] Heather E. Whitson,[26,27] and Raymond Yung,[28,29,30]

[1]Division of Geriatrics and Clinical Gerontology, National Institutes of Health, National Institute on Aging, Bethesda, Maryland; [2]Department of Medicine, Center on Aging, University of Connecticut Health Center, Farmington; [3]Department of Epidemiology, University of Pittsburgh Graduate School of Public Health and [4]Department of Medicine, Division of Geriatric Medicine, University of Pittsburgh School of Medicine, Pennsylvania; [5]Department of Internal Medicine, Section of Geriatrics, Yale University School of Medicine, New Haven, Connecticut; [6]Department of Immunology, Center on Aging, University of Connecticut Health Center, University of Connecticut, Farmington; [7]Department of Psychology, University of Notre Dame, Indiana; [8]R. D. Berlin Center for Cell Analysis and Modeling, University of Connecticut School of Medicine, University of Connecticut, Farmington; [9]Duke University School of Medicine, Duke University Medical Center and [10]Durham VA Geriatric Research Education and Clinical Center, North Carolina; [11]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University, California; [12]Department of Medicine, Division of Geriatric Medicine, Vanderbilt University School of Medicine, Vanderbilt University Nashville, Tennessee; [13]Office of the Scientific Director, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; [14]Robert and Arlene Kogod Center on Aging, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota; [15]Department of Gerontology and Geriatrics, Sticht Center on Aging, Wake Forest University School of Medicine, Winston-Salem, North Carolina; [16]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston and [17]Institute for Aging Research, Hebrew Senior Life, Boston, Massachusetts; [18]Division of Geriatric Medicine, Department of Internal Medicine, School of Medicine, University of Washington, Seattle; [19]Division of Geriatric Medicine, Department of Medicine, School of Medicine, Duke University and [20]Department of Veterans Affairs Medical Center, Durham, North Carolina; [21]Division of Aging Biology, National Institute on Aging, National Institutes of Health, Bethesda and [22]Longitudinal Studies Section, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; [23]Center on Aging and Health, [24]Division of Biostatistics and Bioinformatics, Department of Oncology, School of Medicine, and [25]Division of Geriatrics Medicine and Gerontology, Department of Medicine, Johns Hopkins University School of Medicine, Johns Hopkins University, Baltimore, Maryland; [26]Duke University Aging Center and [27]Geriatric Research, Education and Clinical Center, Durham Veterans Affairs Medical Center, North Carolina; [28]Division of Geriatric and Palliative Medicine, Department of Internal Medicine, School of Medicine and [29]Graduate Program in Immunology, University of Michigan; and [30]Geriatric Research, Education and Clinical Care Center (GRECC), VA Ann Arbor Health System, Michigan

Address correspondence to Anne B. Newman, MD, MPH, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, A527 Crabtree Hall,130 DeSoto Street, Pittsburgh, PA 15261. E-mail: newmana@edc.pitt.edu

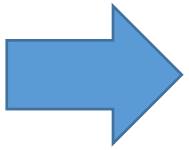
Received September 16, 2016; Editorial Decision Date December 21, 2016

Decision Editor: Stephen Kritchevsky, PhD

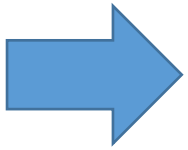
A Conceptual Model

REAL-WORLD STRESSOR; e.g.:

- Hip fracture
- Myocardial infarction
- Infection
- Chemotherapy
- Surgery
- Death of spouse/child
- Divorce
- Verbal/emotional abuse



Physiologic/ Behavioral Responses



OUTCOMES; e.g.:

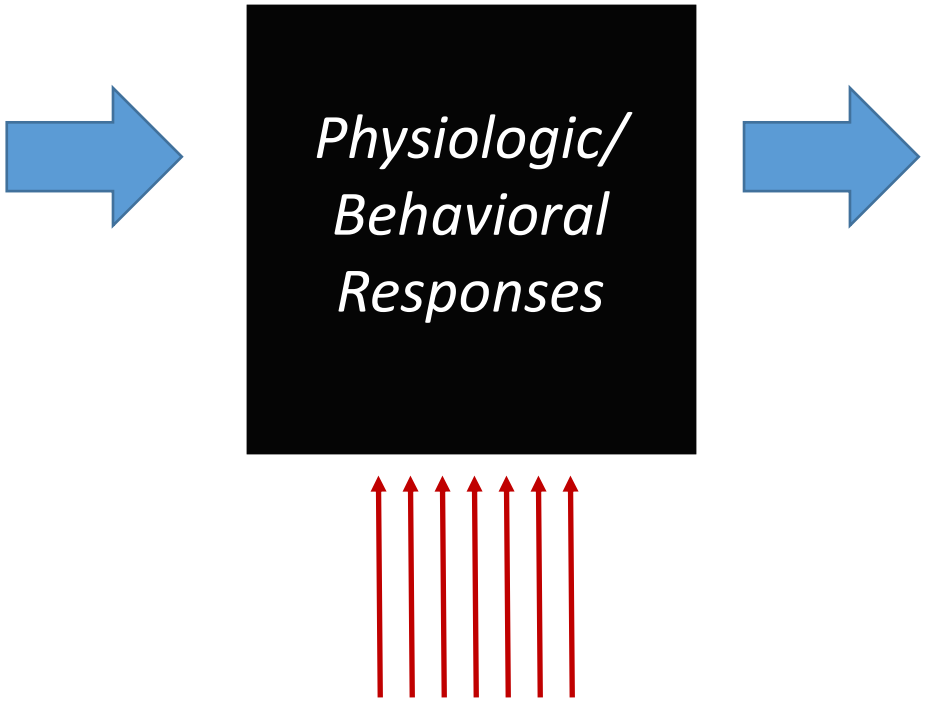
- Survival
- Functional status
- Symptoms
- Indicators of health or disease
- Health-related quality of life
- Subjective well-being

Resiliencies

A Conceptual Model

REAL-WORLD STRESSOR; e.g.:

- Hip fracture
- Myocardial infarction
- Infection
- Chemotherapy
- Surgery
- Death of spouse/child
- Divorce
- Verbal/emotional abuse

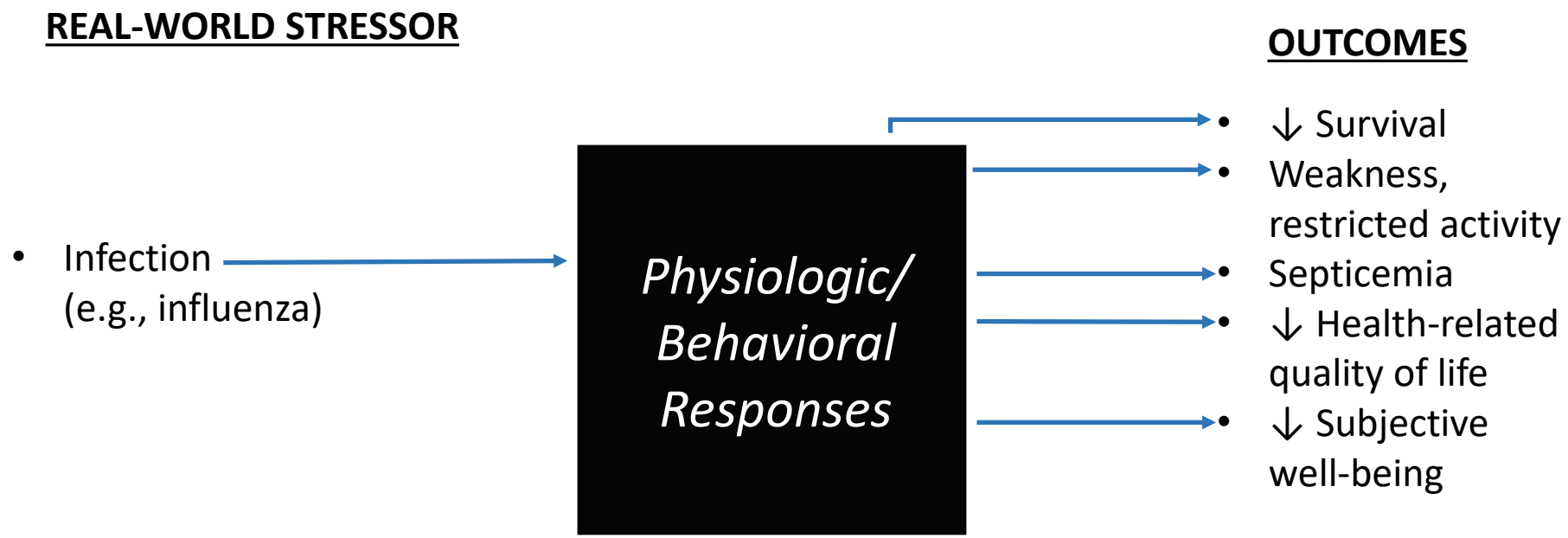


OUTCOMES; e.g.:

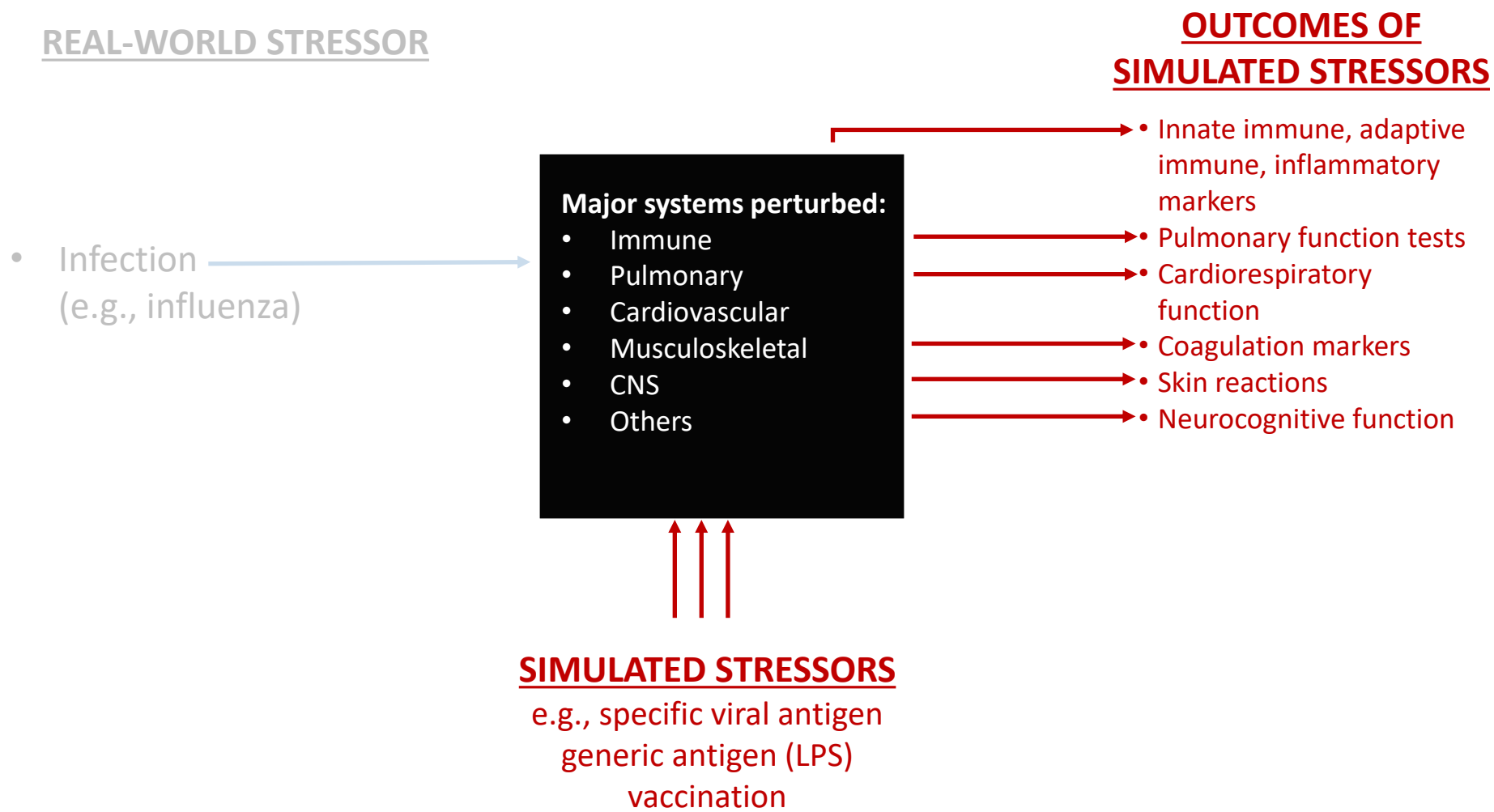
- Survival
- Functional status
- Symptoms
- Indicators of health or disease
- Health-related quality of life
- Subjective well-being

Simulated stressor can perturb the same response systems as a real-world stressor

An example



Simulated stressor can perturb the same response systems as a real-world stressor



Why Measure Resiliencies?

- Resiliencies are **clinically meaningful in themselves**: determine survival, maintenance of function, duration of illness, suitability for aggressive medical or surgical procedures.
- Better tests of resiliencies could **improve clinical management** of older patients, e.g.,., inform choice of treatments.
- Resilience measures can **predict future health outcomes** (short- and long-term).
- Insight into changes in resiliencies across the human lifespan could **reveal aging mechanisms** underlying decrements, as well as factors contributing to the maintenance of resilient phenotypes.
- Characterizing physiologic responses and their underlying cellular mechanisms could lead to the **identification of novel therapeutic targets and interventions to enhance resiliencies.**
- Better predictive tests for resilience could be used as **surrogate markers of intervention trials to improve resiliencies.**

What is resilience?

What is health?

Trans-NIH resilience working group

https://ods.od.nih.gov/Research/resilience.aspx